10/829,411
JAN

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/495 — A1

(11) International Publication Number: **WO 98/52568**

(43) International Publication Date: 26 November 1998 (26.11.98)

(21) International Application Number: PCT/EP98/02852

(22) International Filing Date: 14 May 1998 (14.05.98)

(30) Priority Data:
MI97A001190 21 May 1997 (21.05.97) IT

(71) Applicant: SCHERING-PLOUGH S.P.A. [IT/IT]; Via Ripamonti, 90, I-20141 Milano (IT).

(72) Inventors: ONGINI, Ennio; Residenza Sorgente, Milano 2, I-20090 Segrate (IT). ADAMI, Marina; Via Ferrandina, 12/A, I-20097 S. Donato Milanese (IT). BERTORELLI, Rosalia; Via Felice Romani, 3/A, I-20125 Milano (IT).

(74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: THE USE OF 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES FOR THE PREPARATION OF MEDICAMENTS USEFUL FOR THE TREATMENT OF CEREBROVASCULAR DISTURBANCES

(57) Abstract

The present invention relates to the use of 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues for the preparation of medicaments for the treatment of cerebrovascular disorders, such as stroke, brain trauma, cerebral infarction and their neurological sequelae.

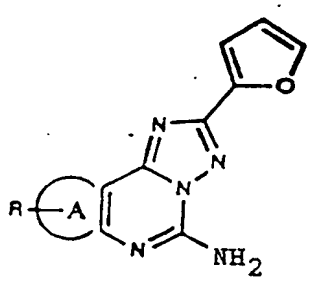
*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# THE USE OF 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES FOR THE PREPARATION OF MEDICAMENTS USEFUL FOR THE TREATMENT OF CEREBROVASCULAR DISTURBANCES

The present invention relates to the use of 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues of formula (I)

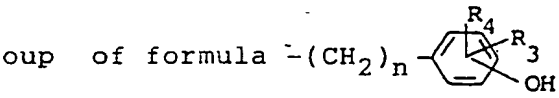


(I)

in which:

A is a pyrazole, imidazole or triazole ring;

R is hydrogen; $C_1$-$C_8$ alkyl; $C_3$-$C_7$ alkenyl, $C_3$-$C_7$ alkynyl; $C_3$-$C_7$ cycloalkyl; $C_1$-$C_5$ alkyl substituted with 1-3 halogen atoms, hydroxy, $C_1$-$C_4$ alkoxy, $C_3$-$C_7$ cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$, wherein $R_1$ and $R_2$, which can be the same or different, are hydrogen, $C_1$-$C_5$ alkyl, $C_7$-$C_{10}$ aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms selected from N, O, S; aryl optionally substituted with halogen atoms, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, carboxy, carboxyamido groups; $C_7$-$C_{10}$ aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a

group of formula  wherein $R_3$ and $R_4$ which can be the same or different, are H, OH, halogen atoms, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, carboxy or carboxyamido groups; moreover the OH group, together with one of $R_3$ or $R_4$, or $R_3$ and $R_4$ together, can form the methylenedioxy group $-O-CH_2-O-$, n is an integer of 0 to 4; a group of formula $-(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer of 1 to 5;

or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cerebrovascular disorders, i.e. in all those brain injuries caused by either impairments of the cerebral circulation or trauma, following deprivation of oxygen and of those nutritional substances which the area vascularized by the vessels involved in the pathological condition is subjected to Stroke, cerebral infarction and brain trauma are among the most severe conditions which can be treated with the medicaments here described.

The compounds of formula (I) are selective antagonists of adenosine $A_{2A}$ receptors.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system,

adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97; Williams M., Adenosine and Adenosine receptors. The Humana Press, 1990).

A number of studies showed adenosine actions are mediated by four subtypes of receptors which are located on the cell membrane: two high-affinity ones, inhibiting the activity of the enzyme adenylate cyclase ($A_1$ and $A_3$ receptors), and two low-affinity ones, stimulating the activity of the same enzyme ($A_{2A}$ and $A_{2B}$ receptors) (J. Med. Chem. 1982, 25, 197-207; Physiol. Rev. 1990, 70, 761-845; J. Med. Chem. 1992, 35, 407-422; Pharmacol. Rev. 1994, 46, 143-156).

Intense research efforts have made it possible to identify and develop analogs of adenosine which are able to interact as selective agonists for the four receptors, including the $A_{2A}$ receptor type (Pharmacol. Rev., 1994, 46, 143-156).

Other studies allowed to develop heterocyclic compounds capable of antagonizing some receptor types. The xanthine compounds, for example, antagonize both $A_1$ and $A_{2A}$ receptors (J. Med. Chem., 1992, 35, 407-422).

As far as the $A_{2A}$ receptor antagonists are concerned, the compounds of general formula (I), which are known to exert a selective action on said receptors,

as well as the process for the preparation thereof, are disclosed in WO 9501356 and WO 9705138 applications. A number of different possible uses of the compounds of formula (I) are cited in said applications, but in no cases a specific use in the treatment of cerebrovascular disorders is described.

Now it has surprisingly been found that compounds of general formula (I) are capable of reducing by more than 40% the total volume of cerebral infarction in animal models in which a focal cerebral ischemia has been induced.

Particularly, the study was carried out on animals (rats) subjected to occlusion of the median cerebral artery (MCA), by electrocauterization and subsequent determination of the cerebral infarction total volume by means of histologic analysis of the brain preparations (Surg. Neurol. 1985, 24:47-51).

Said models are considered relevant to cerebrovascular pathologies in humans.

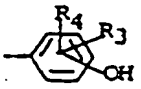
Although other heterocyclic compounds (CGS 15943 and CP66713, respectively; Life Sciences, 55, 61-65, 1994 and Brain Research 705, 79-84, 1995) are known to act favourably in cerebral ischemia animal models, nevertheless such compounds act as non-selective antagonists of the $A_{2A}$ receptors, in that they also block other adenosine receptor subtypes thus causing undesired side-effects.

On the contrary, the compounds of formula (I) showed a high affinity for $A_{2A}$ receptors and a remarkable selectivity compared with the other receptors subtypes, having, for instance, a $A_{2A}$ receptor affinity

up to 800-fold higher than the affinity to $A_1$ receptors, therefore being safer and more suitable even for a long-term treatment of disturbances due to cerebrovascular pathologies.

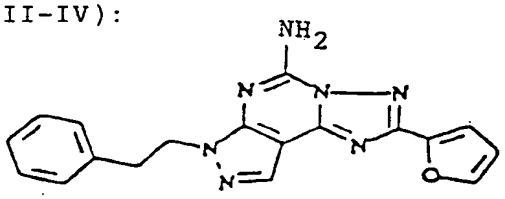
Particularly effective and therefore preferred are those compounds of formula (I) wherein:

A is pyrazole, imidazole or triazole;

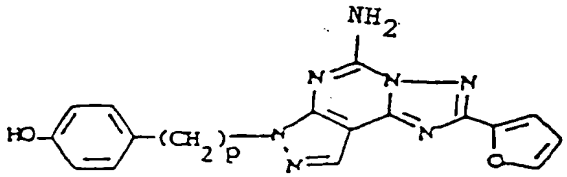
R is $C_7$-$C_{10}$ aralkyl or the group $-(CH_2)_n$-  wherein

$R_3$ and $R_4$, which can be the same or different, are hydrogen, OH, halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkoxy, $C_1$-$C_4$ haloalkyl, carboxy or carboxyamido; moreover the OH group, together with one of $R_3$ or $R_4$, or $R_3$ and $R_4$ together, can form the methylenedioxy group $-O-CH_2-O-$; n is an integer of 0 to 4,

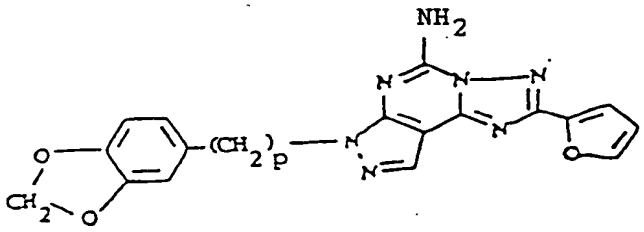
most preferred are the compounds having the following formulae (II-IV):



(II)



(III)



(IV)

wherein p = 2 or 3.

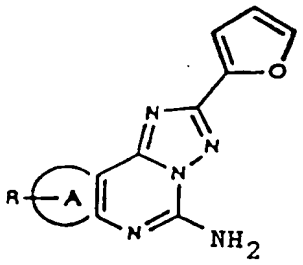
For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical compositions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, 17th ed., 1985.

The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0.01 to 1 mg/kg body weight.

Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (plasters) and the like.

CLAIMS

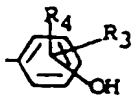
1. The use of the compounds of formula I:



(I)

in which:

A is a pyrazole, imidazole or triazole ring;

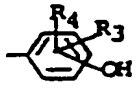
R is hydrogen; $C_1$-$C_8$ alkyl; $C_3$-$C_7$ alkenyl, $C_3$-$C_7$ alkynyl; $C_3$-$C_7$ cycloalkyl; $C_1$-$C_5$ alkyl substituted with 1-3 halogen atoms, hydroxy, $C_1$-$C_4$ alkoxy, $C_3$-$C_7$ cycloalkyl, groups of formula $-NR_1R_2$, $-CONR_1R_2$, wherein $R_1$ and $R_2$, which can be the same or different, are hydrogen, $C_1$-$C_5$ alkyl, $C_7$-$C_{10}$ aralkyl, phenyl, or taken together with the nitrogen atom they are linked to, they form an azetidine ring or a 5-6 membered heterocyclic ring containing one or more heteroatoms selected from N, O, S; aryl optionally substituted with halogen atoms, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, carboxy, carboxyamido groups; $C_7$-$C_{10}$ aralkyl in which the aryl moiety can be substituted with one or more of the substituents indicated above for the aryl group; a group of formula $-(CH_2)_n$-  wherein $R_3$ e $R_4$ which can be the same or different, are H, OH, halogen

atoms, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkyl, $C_1$-$C_4$ haloalkoxy, carboxy or carboxyamido groups; moreover the OH group, together with one of $R_3$ or $R_4$, or $R_3$ and $R_4$ together, can form the methylenedioxy group -O-$CH_2$-O-, n is an integer of 0 to 4; a group of formula -$(CH_2)_m$-Het, wherein Het is a 5-6 membered aromatic or non aromatic heterocyclic ring containing one or more heteroatoms selected from N, O, S and m is an integer of 1 to 5;

or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of cerebrovascular disorders, such as stroke, cerebral infarction and brain trauma.

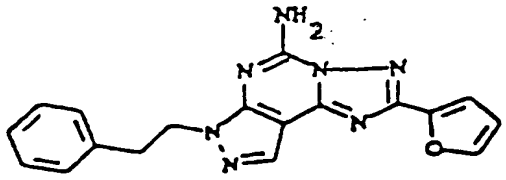
2. The use according to claim 1 of the compounds in which:

A is pyrazole, imidazole or triazole;

R is $C_7$-$C_{10}$ aralkyl or the group -$(CH_2)_n$-  wherein

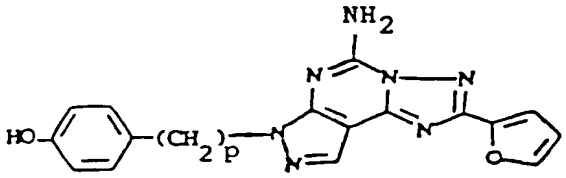
$R_3$ and $R_4$, which can be the same or different, are hydrogen, OH, halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ alkyl, nitro, amino, cyano, $C_1$-$C_4$ haloalkoxy, $C_1$-$C_4$ haloalkyl, carboxy or carboxyamido; moreover the OH group, together with one of $R_3$ or $R_4$, or $R_3$ and $R_4$ together, can form the methylenedioxy group -O-$CH_2$-O-; n is an integer of 0 to 4.

3. The use according to claim 2 of the compound of formula (II)



(II)

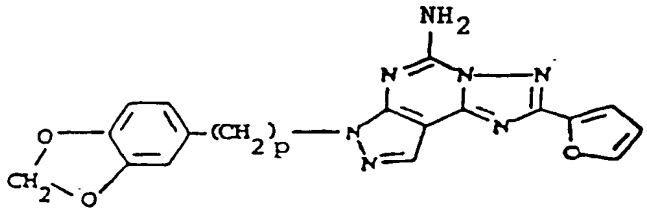
4. The use according to claim 2 of the compounds of formula (III)



(III)

wherein p = 2 or 3.

5. The use according to claim 2 of the compounds of formula (IV)



(IV)

wherein p = 2 or 3.

# INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/EP 98/02852

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,P | ONGINI: "a selective a(2a) adenosine receptor antagonist" DRUG DEV. RES., vol. 42, no. 2, October 1997, pages 63-50, XP002076516 see page 68, right-hand column, paragraph 2 --- | 1-5 |
| X,P | BONA ET AL.: "neonatal cerebral hypoxia-ischemia: the effect of adenosine receptor antagonists" NEUROPHARMACOLOGY, vol. 36, no. 9, September 1997, pages 1327-1338, XP002076517 see page 1335, left-hand column, paragraph 2 --- -/-- | 1-5 |

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 4 September 1998 | 21/09/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Trifilieff-Riolo, S |

1

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 98/02852

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | BARALDI ET AL: "pyrazolo(4,3-3)-1,2,4-triazolo(1,5-c)pyrimidine derivatives: potent and selective a2a adenosine antagonists" J MED CHEM, vol. 39, no. 5, 1996, pages 1164-1171, XP002076518 see page 1167 --- | 1-5 |
| A | DIONISOTTI ET AL.: "effects of the new a2 adenosine receptor antagonist 8fb-ptp an 8 substituted pyrazolo-triazolo-pyrimidine on in vitro functional models" BR J PHARMACOL, vol. 112, no. 2, 1994, pages 659-665, XP002076519 see page 664, right-hand column ----- | 1-5 |

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Ir. .ational application No.
PCT/EP 98/02852

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
In view of the large number of compounds which are defined by the wording of the claims, the search has been performed on the general idea and compounds mentioned in the examples of the description.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.